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Cerebral Small Vessel Disease Burden Predicts Neurodegeneration and Clinical Progression in Prodromal Alzheimer's Disease

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Abstract.

Background: Cerebral small vessel disease (CSVD) has been suggested to contribute to the pathogenesis of Alzheimer's disease (AD).

Objective: This study aimed to comprehensively investigated the associations of CSVD burden with cognition and AD pathologies.

Methods: A total of 546 non-demented participants (mean age, 72.1 years, range, 55–89; 47.4% female) were included. The longitudinal neuropathological and clinical correlates of CSVD burden were assessed using linear mixed-effects and Cox proportional-hazard models. Partial least squares structural equation model (PLS-SEM) was used to assess the direct and indirect effects of CSVD burden on cognition.

Results: We found that higher CSVD burden was associated with worse cognition (MMSE, $\beta = -0.239$, $p = 0.006$; MoCA, $\beta = -0.493$, $p = 0.013$), lower cerebrospinal fluid (CSF) Aβ level ($\beta = -0.276$, $p < 0.001$) and increased amyloid burden ($\beta = 0.048$, $p = 0.002$). In longitudinal, CSVD burden contributed to accelerated rates of hippocampus atrophy, cognitive decline, and higher risk of AD dementia. Furthermore, as the results of PLS-SEM, we observed both significant direct and indirect impact of advanced age (direct, $\beta = -0.206$, $p < 0.001$; indirect, $\beta = -0.002$, $p = 0.043$) and CSVD burden (direct, $\beta = -0.096$, $p = 0.018$; indirect, $\beta = -0.005$, $p = 0.040$) on cognition by Aβ-p-tau-tau pathway.

Conclusion: CSVD burden could be a prodromal predictor for clinical and pathological progression. Simultaneously, we found that the effects were mediated by the one-direction-only sequence of pathological biomarker changes starting with Aβ, through abnormal p-tau, and neurodegeneration.

Keywords: Alzheimer's disease, cerebral small vessel disease, cerebrospinal fluid biomarkers, cognition, partial least squares structural equation pathway model

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[1]Data used in preparation of this paper were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or in the writing of this paper. A complete listing of ADNI investigators can be found at https://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

INTRODUCTION

The amyloid cascade hypothesis was proposed to explain the core cause of Alzheimer's disease (AD) in the past decades. According to the hypothesis, amyloid-β (Aβ) accumulation is the earliest pathological event and is followed by phosphorylated tau (p-tau) accumulation and neurodegeneration. It has been recognized that the presence of Aβ is known as the main AD pathological change before the appearance of cognitive and behavioral impairments during the long asymptomatic phase of AD [1, 2].

Cerebral small vessel disease (CSVD) comprises a variety of disorders affecting small arteries and microvessels of the brain, mainly manifesting as white matter hyperintensities (WMH), cerebral microbleeds (CMBs), and lacunar infarcts (LIs). CSVD and AD frequently co-exist and both are causes of dementia [3]. Actually, CSVD, as a dynamic whole-brain disease, affects almost everyone older than 90 years and contributes to 45% of dementia cases and global functional decline [4]. A large autopsy-based neuropathological consensus report revealed that 80% of AD patients (no evidence of vascular dementia) had vascular pathology including CSVD, suggesting that cerebrovascular dysfunction is a prominent feature of AD and may lower the threshold for dementia for a given AD pathology burden [5, 6]. Although it is well known that the impact of vascular health on cognition is mediated via vascular brain injury [7], the direct effect of vascular health on the AD pathology process remains debated. Besides, age is a significant driver of the decline in vascular health and increase in AD pathophysiology, acting through several biological mechanisms at the cellular or tissue level that may lead to multi-system loss of function.

In the study, we aimed to comprehensively investigate the associations of CSVD burden with cognition and AD pathologies. Simultaneously, we hypothesized that the effects of CSVD burden and AD risk factors on cognition were mediated by the one-direction-only sequence of pathological changes starting with Aβ, followed by abnormal p-tau, and eventually neurodegeneration. Therefore, we performed a set of analyses: 1) to investigate the relationships of CSVD burden with AD core biomarkers and cognition impairment; 2); to investigate the relationship of CSVD burden with cognitive decline and whether CSVD burden could accelerate clinical progression 3) to test the contributions of CSVD burden and risk factors to cognition impairment across the AD continuum in non-demented elderly individuals.

MATERIALS AND METHODS

Subjects

Data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). As a public-private collaboration, the ADNI project began in 2003 designed to measure the progression of mild cognition impairment (MCI) and early AD through investigating clinical, imaging, genetic, biological markers, and neuropsychological measures. This multi-centered research project was approved by institutional review boards at each site and it has obtained written informed consent from all participants or surrogates. Detailed information can be found at https://adni.loni.usc.edu/study-design.

Five hundred and forty-six non-demented individuals aged 55 to 90 from the ADNI database were initially selected as they provided both cerebrospinal fluid (CSF) and imaging core biomarkers, CSVD data (and some other vascular risk factors), and general or composite cognitive scores for cross-section analyses. Apart from the ADNI exclusion criteria, we also excluded participants with a baseline diagnosis of AD to avoid the influence of complex conditions on the results. In addition, MCI subjects were diagnosed with a Mini-Mental State Examination (MMSE) score of 24 to 30, an objective memory loss tested by delayed recall of the Wechsler Memory Scale logical memory II (>1 SD below the normal mean), a Clinical Dementia Rating scale Sum of Boxes (CDR-SB) score of at least 0.5, preserved activities of daily living, and absence of dementia. Cognition normal (CN) was defined as those who had an MMSE score of 24 or higher and a CDR-SB score of 0 [8–10]. A cut-off of 65 years was used to identify the participants in midlife ($n = 84$) or late life ($n = 462$) for subgroup analyses. In the longitudinal analyses, to reserve the sample size and evaluate the longitudinal association of CSVD and cognition, 637 participants who provided both follow-up CSVD data and cognitive scores were included, though these participants may lack of data on core biomarkers of AD.

CSF biomarkers and PET imaging measures

The CSF procedural protocols have been described previously [11]. In brief, CSF Aβ, p-tau, and t-

tau were measured using the INNOBIA AlzBio3 immunoassay (Fujirebio, Belgium) on the xMAP platform (Luminex). The process of sample measurement and quality control met the acceptance criteria according to the Roche Protocol in the UPenn/ADNI Biomarker Laboratory [12].

The positron emission tomography (PET) data used were from the UC Berkeley and Lawrence Berkeley National Laboratory. Brain amyloid burden was measured via flobetapir (AV45) SUVR, which was calculated by averaging the values across four cortical regions, with the whole cerebellum as the reference region.

Acquisition of MRI data

All magnetic resonance imaging (MRI) data were obtained in 1.5-Tesla and 3.0-Tesla scanner systems at each ADNI site according to a standardized protocol. Detailed information of the parameters can be found at https://adni.loni.usc.edu/methods/mri-tool/mri-analysis.

Assessment of hippocampus

The regional volume estimates for the 1.5 and 3.0 T MRI images were processed with the Free-surfer software package version 4.3 and 5.1 image processing frameworks, respectively (https://adni.loni.usc.edu/). The MRI T1-weighted image underwent initial preprocessing, intensity normalization, and gradient expansion. The volume structures of subcortical white matter and deep gray matter were segmented by automatic Talairach transform after a hybrid watershed/surface deformation removed the non-brain tissue. The hippocampus was selected as the region of interest.

Assessment of CMBs

CMBs were defined as small homogenous hypointense lesions with a diameter of 2 to 5 mm generally, occasionally up to 10 mm, seen on T2*-weighted MRI or other sensitive sequences [13, 14]. All available T2* scans of individuals were used for identifying the numbers and locations of CBMs by trained image analysts and further confirmed by radiologists experienced in reading T2* images. Only the definite status was included in the current study and finally was categorized as present if there was at least 1 visible lesion, or absent if there was no visible lesion [8].

Assessment of WMH

The quantification of WMH has been detailed described in a previous essay [15]. Briefly, structural brain images were measured through the Bayesian approach for the segmentation of high-resolution 3-dimensional magnetization prepared rapid gradient echo T1-weighted and T2-FLAIR sequences [16]. In the present study, the Fazekas rating scale was used to assess WMH, which was calculated as a sum of periventricular and deep WMH scores ranging from 0 to 6, identified by two experienced radiologists in reading T1-weighted and T2-FLAIR images.

Assessment of LIs

LIs were defined as CSF-like hypointensity, which a diameter between 3 mm to 15 mm with a surrounding rim of hyperintensities in T2-FLAIR data. Also two trained radiologists identified Lacune by reading T2-FLAIR images. Lacune was recorded as present if there was at least 1 Lacune lesion visible, or absent if there was no Lacune lesion visible [17].

Assessment of CSVD burden

Lacunes, WMH, and CBMs have been identified as MRI markers of CSVD burden in current study [13, 18]. According to the published simple MRI CSVD score based on visual rating [19], the presence of CMBs, a Fazekas score of $\geq$2, and a LIs count of $\geq$3 scored one point respectively, generating a simple CSVD score range of 0 to 3. As for CSVD amended score, WMHs were graded from 0 to 3 using the Fazekas scale (0, 1, 2 = 0, 1, 2 respectively, 3 = >3), and the number of LIs was scaled from 0 to 3 (0 = none, 1 = 1 to 2, 2 = 3 to 5, 3 = >5). one point was assigned for the presence of CMBs, 3 points each for Fazekas score and LIs, resulting in a score among 0 to 7 [19]. We further divided participants into CSVD group (simple score >1) and non-CSVD group (simple score = 0) according to their simple CSVD scores.

Cognitive assessments

We used multiple scales to assess cognitive functions, including MMSE, the Montreal Cognitive Assessment Scale (MoCA), and the cognitive section of Alzheimer's Disease Assessment Scale with 11 items (ADAS). Participants also underwent neuropsychological assessments of cog-

nitive domains (executive, memory, language, and visuospatial functions) by reviewing the neuropsychological batteries to identify items that could be considered as the indicators of these domains [20, 21]. Lower composite scores indicated worse cognitive status. The above mentioned scales were used to separately assess general and specific cognition functions [8].

Statistical analyses

We tested for normality of the distribution of each AD biomarker using "car" package in R software. Data were presented as mean ± SD or percentage (%) where appropriate. The comparisons of cognition and biomarkers between CSVD and normal groups were conducted using Wilcoxon test or *t*-test. We conducted linear regression models with global and composite cognition scores and AD biomarkers as variables of interest (dependent variables), and CSVD burden as the independent variable. Age, gender, education, and *APOE* ε4 status were added as covariates for all the models. Interaction terms for main AD risk factors (age, gender, and *APOE4* status) were used to explore whether strata effect existed. Subgroup analysis was stratified by age. Sensitivity analyses were performed by adding more covariates, including hypertension (yes or no), hyperlipemia (yes or no), diabetes mellitus (yes or no), coronary heart disease (yes or no), cigarette use (yes or no), and alcohol use (yes or no).

Furthermore, the linear mixed effects (LME) models were conducted to depict the longitudinal influences of CSVD burden on biomarkers and cognition. We treated CSVD scores as independent variables, and treated biomarkers and cognitive measurements as dependent variables. The LME models had random intercepts and slopes for time and unstructured covariance matrix for the random effects, as well as the interaction between time and the independent variable as a predictor. The above regression analyses were repeated using WMH Fazekas cores and volumes, CMBs, and LIs as independent variables.

To evaluate the risk of clinical progression, we plotted Kaplan-Meier survival curves and computed hazard ratios in the Cox proportion-hazards models. The adjusted risk, expressed as hazard ratio (HR) and 95% confidence interval (CI), was estimated for the association between incident AD and CSVD burden. Individuals who did not develop AD or who were lost to follow-up were censored at the time of their last evaluation. The dependent variable was time from entry into the cohort to AD diagnosis.

Finally, we performed partial least squares structural equation modeling (PLS-SEM) to assess the direct and indirect effects of observed and latent variables of AD biomarkers, AD related risk factors (age, gender, education level, *APOE4* genotype) as well as CSVD burden on cognitive outcome measures. The biomarker pathways were *a priori* hypothesized as illustrated in Supplementary Figure 3. Basic risk factors, CSVD burden, and AD core pathology were manifest variables and cognition was latent variable. PLS-SEM allows assessment of inter-construct relationships as well as relationships among constructs and their respective indicators. Total variance in cognition accounted for by the overall PLS-SEM fit was computed using Wright's rules for the coefficient of determination (R^2) calculation [22].

We mainly used R software (version 3.5.1) for the statistical analyses and figure preparation. Packages "car", "ggplot2", "ggpubr", "magrittr", "survminer", and "lme4" were used in the study. In addition, the SmartPLS version 3 software was used to perform the PLS-SEM analysis. A two-sided p value <0.05 was considered significant.

RESULTS

A total of 546 non-demented individuals consisting of 377 MCI and 169 CN were included. Demographics, AD biomarkers, cognition measurements, as well as CSVD burden and components were summarized in Table 1. As for those who provided CSVD data, the mean (SD) age was 72.1 (SD = 7.0) years old, with a male proportion of 52.6% and an *APOE* ε4 carrier proportion of 41.0%.

Associations of CSVD burden with AD biomarkers and cognition

Participants with CSVD had lower cognitive scores and Aβ levels, as well as higher levels of tau-related biomarkers, compared with non-CSVD individuals. Moreover, the *post hoc* analysis based on the severity of CSVD found that participants with more severe CSVD burden had more significant cognitive impairment and AD pathologies (Supplementary Figure 1). Nevertheless, when we treated simple scores or amend scores as dependent variables in linear regression models, their association with Aβ but not with tau-related biomarkers were still significant, after adjusting for confounding factors. The results were

Table 1
Participants' demographics and cognitive measures

No	WMH (Fezakas) N = 682	CMB N = 659	LIs N = 893	CSVD N = 546
Age (y range)	72.1 ± 6.8	72.0 ± 6.8	72.9 ± 7.04	72.1 ± 7.0
Female, *n* (%)	332 (48.6%)	322 (48.84%)	394 (44.12)	259 (47.4%)
Education (years)	16 (14-18)	16 (14-18)	16 (14-18)	16 (14-18)
APOE ε4 carriers *n* (%)	278 (40.7%)	272 (41.27%)	377 (42.21%)	224 (41.0%)
Hypertension *n* (%)	292 (42.81%)	281 (42.64%)	374 (41.88%)	230 (42.12%)
Hyperlipidemia *n* (%)	349 (51.17%)	333 (50.53%)	418 (46.80%)	272 (49.81%)
Coronary heart disease *n* (%)	38 (5.57%)	36 (5.46%)	40 (4.47%)	29 (5.31%)
Diabetes *n* (%)	70 (10.26%)	70 (10.62%)	84 (9.40%)	53 (9.70%)
Smoking *n* (%)	177 (25.95%)	172 (26.10%)	255 (28.55%)	143 (26.19%)
Drinking *n* (%)	13 (1.90%)	13 (1.97%)	24 (2.69%)	10 (1.83%)
Aβ (pg/mL)	183.5 ± 52.2	183.2 ± 52.0	180.7 ± 53.9	182.0 ± 52.3
p-tau (pg/mL)	38.8 ± 22.7	38.9 ± 22.9	36.6 ± 21.6	38.6 ± 21.6
Tau (pg/mL)	78.2 ± 46.4	78.4 ± 46.6	83.2 ± 48.0	80.6 ± 48.1
AV45	1.18 ± 0.22	1.18 ± 0.21	1.18 ± 0.21	1.18 ± 0.21
Hippocampus volume (mm^3)	7223 ± 1048	7229 ± 1055	7051 ± 1080	7199 ± 1044
Intracranial volume (mm^3)	1504801 (156149)	1505220 (156635)	1523690 (163416)	1504037 (156994)
MMSE	28.4 ± 1.6	28.4 ± 1.6	28.1 ± .17	28.4 ± 1.6
MoCA	24.2 ± 3.1	24.2 ± 3.0	24.0 ± 3.1	24.1 ± 3.1
ADAS	12.6 ± 6.6	12.6 ± 6.6	13.9 ± 6.9	12.9 ± 6.7
MEM	0.62 ± 0.70	0.61 ± 0.73	0.46 ± 0.75	0.58 ± 0.73
EF	0.56 ± 0.90	0.57 ± 0.89	0.41 ± 0.90	0.54 ± 0.88
LAN	0.52 ± 0.78	0.53 ± 0.78	0.41 ± 0.79	0.51 ± 0.77
VS	0.07 ± 0.68	0.08 ± 0.68	0.02 ± 0.71	0.07 ± 0.68
CSVD measures				
Simple scores				0.79 ± 0.81
0*	0	0	<2	247 (42.8%)
1*	>2	1	>3	211 (36.5%)
2-3*	–	–	–	118 (20.4%)
Amended scores				1.83 ± 1.75
0*	0	0	0	161 (27.9%)
1*	1	1	1	125 (21.6%)
2*	2	1	1	95 (16.4%)
3–5*	3	1	2	178 (30.8%)
>5*	3	1	3	17 (2.9%)

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ADAS, Alzheimer's Disease Assessment Scale; MEM, memory function; EF, executive function; LAN, language function; VS, visual function; Aβ, amyloid-β; p-tau, phosphorylated tau; Tau, total tau; AV45, Florbetapir; WMH, white matter hyperintensity; CMB, cerebral microbleeds; LIs, lacunar infarctions; In the simple scores: One point was given for the presence of each of any lacunar infarct, WMH, and CMB. In the amended scores: WMH were graded from 0 to 3 using the Fazekas scale; The number of lacunar infarcts was graded from 0 to 3 (0 = none, 1 = 1 to 2, 2 = 3 to 5, 3 = >5). CMB were graded as absent (0) or present (1). *represented simple and amended scores or the number of lesions.

barely changed in the sensitive analyses (Supplementary Tables 1 and 2). Simple scores, amended scores and Fezakas scores showed significant correlations with all the included cognitive scale scores, and the existence of CMBs and a greater number of LIs were associated with worse cognition.

Among the interaction analyses (Supplementary Table 3), we found that the age*simple score interaction was significantly associated with cognition, including executive function ($p = 0.032$) and language function ($p < 0.001$). On the contrary, the gender*simple score interaction and *APOE4* status*simple score interaction showed no significant associations with cognition and AD core biomarkers. We further stratified participants by age and found that the above differences in cognition and biomarkers remained significant only participants in late life (Fig. 1).

Longitudinal relationship between CSVD and cognition

The longitudinal relationships of CSVD burden with neurodegeneration and cognition were explored in participants who provided intact related data. Totally 637 individuals were included in the analyses and the average follow-up time was 4.68 years (range from 1–10 year). As the results demon-

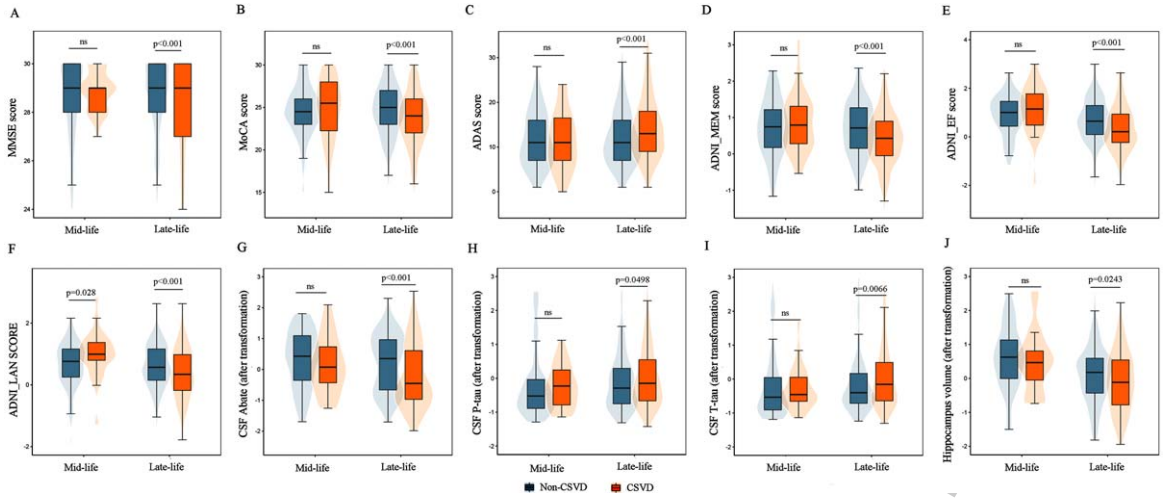

Fig. 1. Differences in cognition and CSF core biomarkers among different groups according to the presence of CSVD. In late-life, participants with CSVD manifested lower cognitive and $A\beta_{42}$ levels and higher tau-related biomarkers levels compared with non-CSVD individuals.

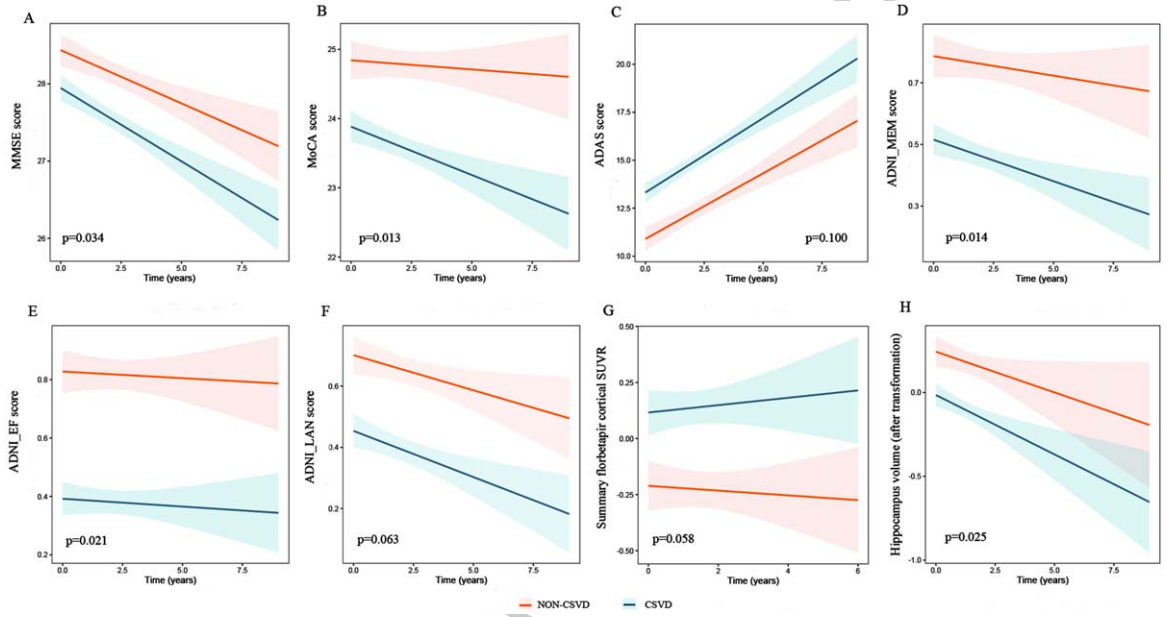

Fig. 2. Longitudinal changes of cognition between cerebral small vessel disease burden (CSVD) and normal individuals. Individuals with CSVD manifested faster cognition deterioration compared with non-CSVD subjects in almost all scales.

strated, CSVD burden accelerated hippocampus atrophy (Fig. 2H). Participants with CSVD showed a faster worsening of general cognition (Fig. 2A, B), memory function (Fig. 2D), and executive function (Fig. 2E) in the future compared with non-CSVD individuals. The deposition of Aβ also displayed a marginally significant increase in CSVD individuals (Fig. 2G). The main results of LME regressions were summarized in Supplementary Table 4. Consistent with the above findings, higher simple scores and amended scores could longitudinally predict worse cognition status as they significantly associated with all cognition measurements (MMSE, MoCA, ADAS, MEM-domain, EF-domain, and LAN-domain, all $p < 0.001$). Furthermore, participants with higher CSVD burden had accelerated rates of cognitive decline and hippocampal atrophy (Supplementary Figure 2). WMH, as represented by Fezakas scores, was also a predictor of cognitive impairments (MMSE, $\beta = -0.072$, $p < 0.001$; MoCA,

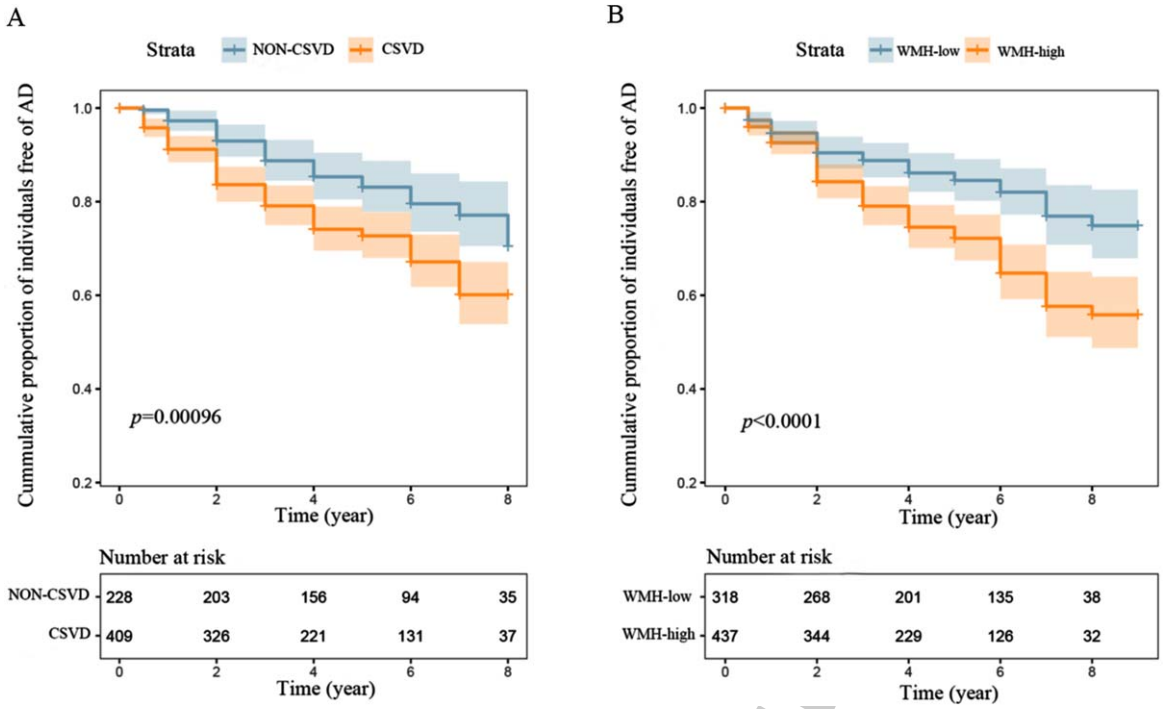

Fig. 3. Kaplan-Meier curves showing survival probability of clinical progression. Progression to MCI/AD, including 1) diagnosed as dementia from baseline MCI individuals; 2) diagnosed as MCI or AD from baseline CN individuals.

β = –0.076, $p < 0.001$; ADAS, β = 0.126, $p = 0.008$; LAN-domain, β = –0.032, $p = 0.028$). In addition, we failed to demonstrate that CMB and LIs could cause a faster cognitive decline.

Prediction of clinical progression

Figure 3 showed the results of the Kaplan-Meier analyses. Individuals with CSVD showed higher conversion risk in clinical progression compared with non-CSVD subjects. Table 2 showed that the progression rate was higher in those with CSVD (27.38%) than non-CSVD individuals (17.98%) (HR = 1.812, 95% CI = 1.266 to 2.592, $p = 0.001$). However, the significance was compromised after adjusting for age, gender, education level, apoe4 status and baseline diagnosis (HR = 1.408, 95%CI = 0.962 to 2.061; $p = 0.076$)).

In addition, survival curves showed significant differences when we compared those with higher Fezakas scores to those with lower scores (we regarded 2 scores as the cutoff value [19]). Compared to those with lower Fezakas scores, individuals with higher scores had an average of 98.8% increased risk of developing AD dementia (HR = 1.988, 95%CI = 1.429 to 2.767; $p < 0.001$).

Results of PLS-SEMs

Figure 4 showed the full constructs of PSL-SEMs and the parameter estimates for the final models. Only the paths that were statistically significant at $p < 0.05$ are represented. The final model fit the data well: the goodness-of-fit (GoF) was 0.54 for the modeling; the standardized root mean square residual (SRMR = 0.045) was less than 0.08; and the normed fit index (NFI = 0.921) was greater than 0.9.

The final PLS-SEM model explained 32.2% of the variance in Aβ, 22.0% in p-tau, 55.2% in tau, and 30% in cognition. CSVD burden, Aβ, p-tau, and tau each independently explained 13.5%, 28.9%, 39.9%, and 11.2% of variance in cognition. In addition, the Aβ-p-tau-tau pathway accounted for 15.4% of variance in cognition. Here we describe some significant independent variables of each outcome in a stepwise fashion. 1) Age was a significant direct risk factor of CSVD burden (β = 0.376, $p < 0.001$), Aβ (β = –0.208, $p < 0.001$), and cognition (β = –0.206, $p < 0.001$). The indirect impact of age on cognition through CSVD burden, Aβ, p-tau, and tau pathologies was also significant (β = –0.002, $p = 0.043$). 2) *APOE4* was a significant direct risk factor of CSVD burden (β = 0.151, $p = 0.001$), Aβ (β = –0.497, $p < 0.001$), p-

Table 2
Progression risk of individuals in present study

	Progression rate	Unadjusted		Adjusted	
		HR (95%)	*p*	HR (95%)	*p*
Progression to MCI/AD					
Non-CSVD	17.98%	ref	–	ref	–
CSVD	27.38%	1.812 (1.266–2.592)	0.001	1.408 (0.962–2.061)	0.076
Progression to MCI/AD					
Fezakas scores (0–2)	16.03%	ref	–	ref	–
Fezakas scores (3–6)	27.23%	1.997 (1.437–2.774)	<0.001	1.988 (1.429–2.767)	<0.001

Event, progression to MCI/AD, including 1) diagnosed as dementia from baseline MCI individuals. 2) diagnosed as MCI or AD from baseline CN individuals. HR, Hazard ratios (95% CI) calculated using Cox regression analyses, in unadjusted and adjusted models corrected for baseline age, gender, *APOE*4 status, and years of education.

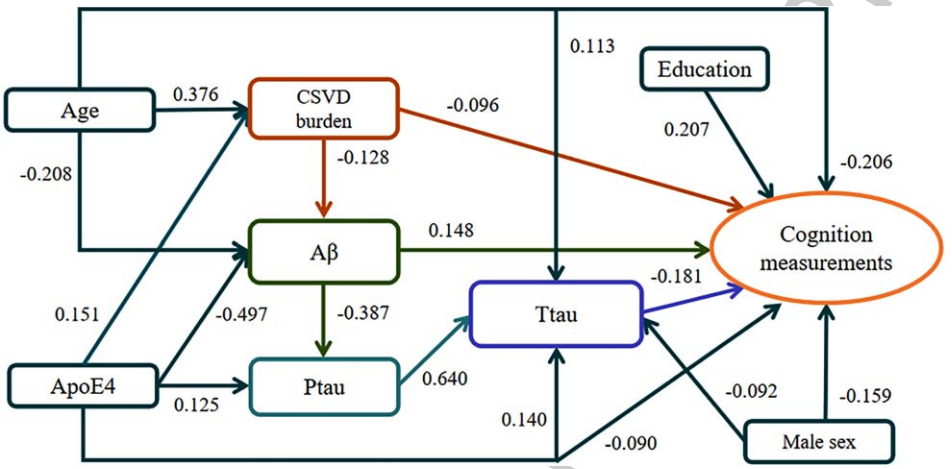

Fig. 4. Results of path analysis of combined AD CSF biomarker pathways mediating the effect of CSVD burden and risk factors on cognitive measurement. Squares or rectangles represent manifest variables. Numbers associated with effects are standardized regression coefficients. Only the paths that were statistically significant at $p < 0.05$ are represented. Paths that were hypothesized but were not statistically significant at $p < 0.05$ are excluded. CSVD burden, CSF Aβ, and Ttau, together with advanced age, presence of *APOE* ε4 allele, lower education level and being male had significant direct effects on greater cognitive impairment. In addition, we also observed that advanced age had significant direct effects on greater CSVD burden, lower CSF Aβ and higher CSF Ttau level. Also, the CSVD burden and biomarker model mediated the effect of age on cognitive impairment. Presence of *APOE* ε4 allele had significant direct effects on greater CSVD burden, lower CSF Aβ level, higher CSF Ptau and Ttau level. But the mediation effect via CSVD burden-Aβ-Ptau-Ttau failed to establish. Greater CSVD burden had significant direct effects on Aβ, but not on Ptau and Ttau. However, the indirect effect of CSVD burden on cognition were significantly through Aβ-Ptau-Ttau. Lowr CSF Aβ had significant direct effects on Ptau but not Ttau.

tau (β = 0.125, $p = 0.004$), tau (β = 0.140, $p < 0.001$), and cognition (β = –0.090, $p = 039$). APOE4, as one of the most definite risk factors of AD, also had significant and direct effects on cognition via the Aβ-p-tau-tau pathway (β = –0.022, $p = 0.008$). 3) Education level was significantly and directly associated with cognition (β = 0.207, $p < 0.001$), and being male was significantly and directly associated with tau (β = –0.092, $p = 0.001$) and cognition (β = –0.159, $p < 0.001$). 4) CSVD burden significantly and directly influenced Aβ (β = –0.128, $p = 0.001$) and cognition (β = –0.096, $p = 0.018$). The indirect impact of CSVD burden on cognition via the Aβ-p-tau-tau pathway was also significant (β = –0.005, $p = 0.040$). In addition, the effect of Aβ-p-tau-tau pathway on cognition was significant, which confirmed the previously proposed AD Aβ cascade hypothesis [23].

DISCUSSION

In this study, we provided sufficient evidence for the associations of CSVD burden with cognition, AD pathologies and clinical progression in prodromal AD. We found that CSVD burden could not only impair cognition, but also intimately lead to abnormal CSF core biomarkers and hippocampus atrophy.

During the long-term follow-up, higher CSVD burden led to accelerated rates of hippocampus atrophy and cognitive decline, as well as a higher risk of AD dementia. Furthermore, as the results of the mediation models indicated, CSF Aβ and tau pathologies, jointly with AD risk factors and CSVD burden, contributed together to cognitive impairment and further decline in non-demented elders.

In our study, higher CSVD burden was associated with lower CSF Aβ level and worse cognition, and it could predict faster declines in global cognition, memory, executive and language functions, as well as greater rates of conversion to AD, but no significant difference was found in tau-related biomarkers between individuals with higher and lower CSVD burden. Up to now, the etiology of CSVD and the mechanisms by which CSVD was involved in cognitive decline and clinical progression of AD are still unclear. Decreased Aβ level is believed to be first in a line of upstream events that cause AD-related dementia. Prior work suggested oxidative stress might be the possible link between AD and the early onset of CSVD [24]. The reactive oxygen species could increase the Aβ deposition formed in the vessel walls or cause the dysfunction of endothelial cells. Further, vascular lesions indeed impaired the Aβ clearance pathway [25]. The above findings suggest that vascular dysregulation may be the early pathological event contributing to the development of AD [26]. Functional changes of the cerebral blood flow caused by structural arterial changes could accelerate Aβ accumulation, thus modifying progression or worsening risk by shifting the threshold for cognitive impairment and AD dementia [27]. Hence, we inferred that CSVD could lead to the slow accumulation of tissue damage, promote amyloid aggregation and restricts its clearance, finally causing abnormal AD pathologies and AD-related cognitive decline in older adults.

The exploratory study of the associations between CSVD burden and AD pathologies was performed in the context of the A/T/N scheme for biomarkers in non-demented elders. The PLS-SEM analyses allowed us to simultaneously observe the direct and indirect effects of risk factors on each variable of interest and also take into consideration the step-wise process of AD progression. The results of PLS-SEM analyses showed that age and CSVD affected cognitive impairment independently or via the Aβ-p-tau-neurodegeneration axis. As reported, advanced age influenced cognitive impairment and decline predominantly and indirectly via greater Aβ burden, greater atrophy, and greater WMH burden [28]. Consistent with this finding, we found evidence for significant direct and indirect impacts of age on cognitive impairment. As the pathway depicted, age increased CSVD burden and decreased CSF Aβ; the joint effects of age and CSVD burden caused abnormal Aβ and tau pathologies, finally leading to cognitive impairment. Moreover, regardless of age, the effects of CSVD burden on cognitive impairment were also mediated via the A/T/N pathway. The widely accepted AD biomarker model demonstrated that Aβ had an initiating role in pathophysiological changes at early stages of AD by facilitating spread and accumulation of tau pathology. Therefore, soluble Aβ changes triggered tau metabolism changes and then the neurodegeneration occurred [29]. Since the effect of aging is inevitable, the joint effect of Aβ and tau pathologies with CSVD on cognition indicates that therapies for vascular protection should take priority over targeted therapies for AD pathologies.

WMH, as a main marker of CSVD, was associated with CSF Aβ and cognitive decline. Higher Fezakas scores also predicted faster conversion to AD. A previous study also demonstrated that WMH influenced cognition via the Aβ-tau-atrophy axis [28]. As reported, WMH led to reduced clearance of brain Aβ through impairment of the glymphatic system [30, 31]. All the above findings suggest the close association between WMH and CSF Aβ. The associations of LIs and CBMs with CSF Aβ remained controversial [31–34], though majority studies held that larger numbers of CBMs and LIs resulted in higher Aβ levels [35, 36]. In present study, we have found baseline associations of cognition with CBMs and LIs, but their longitudinal associations were not significant.

Our study performed a more comprehensive analysis aimed to investigate the associations between CSVD burden and AD pathology, as well as the possible pathways. We mainly focused on the prodromal individuals. These individuals with higher CSF Aβ level resulting in an increased statistical power to detect the earliest changes in the AD continuum. Nevertheless, there are limitations in this study. Firstly, significant associations of baseline levels of CSVD were detected, but there was a lack of data about some markers including enlarged perivascular spaces and brain atrophy in the ADNI database. Secondly, we established the CSVD-Aβ-p-tau-tau-cognition pathway in CSF biomarkers. And further studies conducted in larger cohorts are still warranted to give more credible evidence in imaging biomarkers.

Conclusions

To sum up, this study comprehensively investigated the associations between CSVD burden and AD cognition and pathologies. We mainly found that CSVD burden could be a prodromal predictor for clinical and pathological progression. Simultaneously, we proved that the effects of CSVD burden on cognition were mediated by the one-direction-only sequence of pathological biomarker changes starting with Aβ, through abnormal p-tau, and neurodegeneration. Therapeutic interventions on lowering the risk of vascular disease might be a rational approach to dispose of both early and late-onset AD dementia. The incorporation of CSVD as a biomarker is legitimately warranted in the biological definition of AD.

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CONFLICT OF INTEREST

JTY is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. The authors declare that they have no competing interests.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-221207.

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